All of the revisions to the claims are fully supported by the original disclosure, and no new matter is introduced. Upon entry of this Amendment, claims 1, 3, 4, 7, 9, 10, 12, 13, 16-20, 22-24, 26 and 27 will be pending. Entry and consideration are requested.

In the Office Action, the Examiner objected to claims 5, 6, 14-16, 21, 26 and 27. By the above amendments we have addressed the Examiner's specific concerns.

Claims 2, 6, 8, 15 and 25 were rejected under 35 U.S.C. 101 as allegedly lacking utility. We strongly disagree with the Examiner that there is no utility or practical use of the S gene segment encoding N protein. However, strictly for the purposes of advancing prosecution we have canceled these claims above. We reserve the right to reintroduce the subject matter of these claims in a continuation application at a later date. But with respect to this present application, this rejection is now believed to be moot.

Claims 1-27 stand rejected under 35 U.S.C. §112, second paragraph. Claims 2, 5, 6, 8, 11, 14, 15, 21 and 25 are canceled hereinabove, and this rejection is therefore moot to the extent that it applies to these claims. We have amended claims 1, 9, 10, 11, 17 and 26 above to specifically address the Examiner's concerns as set forth in the action. Consequently, withdrawal of this rejection is believed to be in order.

Claims 1, 9, 10, 17-20, 26 and 27 were rejected under §112, first paragraph as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey that the inventor had possession of the invention as claimed. Again, we disagree with the Examiner that the specification would not demonstrate to someone having skill in this art that the inventors fully possessed the invention as claimed at the time of the invention. However, strictly for the purposes of advancing prosecution we have amended independent claims 1, 9, 17, and 26 to specify that the protein coding region encodes an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one antigenic determinant of a hantavirus protein. This subject matter was contained in claims not part of this rejection—and thus considered to have met the requirements of §112, first paragraph—and consequently these amended claims should address this rejection to the Examiner's satisfaction.

Claims 1-4, 6, 8-10, 12, 13, 15, 17-20, and 25-27 were rejected under §112, first paragraph as non-enabled. The Examiner has taken the position that these claims are

only supported by the specification for "compositions or methods for use in mice or hamsters comprising protein coding region determinants from the M gene segments of the SEOV hantavirus", as well as the Hantaan virus and Dobrava virus. We note that all the independent claims (claims 1, 9, 17 and 26) now specifically recite that the protein coding region encodes an M gene segment protein comprising the sequence set forth in SEQ ID NO:1. This is believed to address most of the Examiner's concerns.

With regard to certain of the Examiner's comments, we respond as follows. The Examiner asserted that the specification fails to provide an enabling disclosure teaching methods of inducing cross-protection against any and all hantaviruses when immunizing with a given M gene segment. Specifically, the Examiner states: "The specification teaches the unpredictability of determining a priori which hantaviral M gene segments can protect against which other hantaviruses." (Office Action, page 7.) However, the genetic relationships of the hantaviruses, as someone having ordinary skill in this art would be aware, indicates otherwise. For example, someone having ordinary skill in this art would reasonably expect that Hantaan, Seoul and Dobrava will be cross-protective because of their close genetic relationship. In contrast, Puumala virus is much less closely related. The first three viruses share >80% amino acid identity in their M segment products, whereas they share only 52% amino acid homology with Puumala virus.

For instance, evidence of this in the art is shown in Xiao, et al., (1994) Phylogenetic Analyses of virus isolates in the genus *Hantavirus*, family *Bunyaviridae*. *Virology*, 198, 205-217, esp. the Figures; Chu et al., (1995) Cross-neutralization of hantaviruses with immune sera from experimentally-infected animals and from hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome patients. *J. Infect. Dis.* 172; 1581*I*; and Chu et al., (1994) Antigenic diversity among viruses in the genus Hantavirus , family Bunyaviridae Virology, 198, 196-204. (We will be providing a copy of these references to the Examiner as soon as possible.) Tables included in the latter two papers demonstrate antigenic and genetic relatedness of Hantaan, Seoul and Dobrava viruses, but not Puumala virus. They also show antigenic relatedness of Black Creek Canal, Sin Nombre, and Puumala viruses. Laguna Negra virus was not included in that study, but can be reasonably inferred from its close genetic relationship to Sin Nombre and Black Creek Canal viruses.

Thus, it is the case that our specification, read with the state of the art in mind, provides an enabling disclosure for reasonable predictability of which hantaviruses can be cross-protected against.

The Examiner also asserted that the specification does not provide an enabling disclosure commensurate with the using the claimed invention to induce protective against any and all mammals. In particular, the Examiner's citations about inability to infer that vaccines that work in hamsters will not work in primates can be refuted based on our clinical studies of a vaccinia vectored vaccine that we tested first in hamsters and then in humans. (McClain, et al., (1999). Phase I and Phase II Clinical Evaluation of a Vaccinia-Vectored Hantaan Virus Vaccine. J Med Virol. 60:77-85. We will be providing a copy of this reference to the Examiner as soon as possible.). Using the same hamster model to measure protection, we found that the vaccine did in fact elicit neutralizing antibodies to Hantaan virus in both hamsters and humans. (An exception was that the vaccine failed to elicit good antibody responses to Hantaan virus in people that were previously vaccinated with vaccinia virus, because of the inability of the recombinant vaccinia virus to grow in the immune individuals). Thus, here again, it is the case that our specification, read with the state of the art in mind, provides an enabling disclosure for reasonable predictability for using the claimed invention to induce protective against all types of mammals.

Reconsideration of this rejection is requested.

Lastly, claims 1-6, 9-13, 15-24, 26 and 27 stand rejected under 35 U.S.C. §103(a) as obvious over Schmaljohn (Rev. Med. Virol. 1994) or Chu et al. (J. Virol. 1995) in view of Montgomery et al. (Pharmacol. Ther. 1997), Donnelly et al. (Ann. Rev. Immunol. 1997) and Arikawa et al. (Virol. 1990). We traverse this rejection for the following reasons.

We first note that all the independent claims (claims 1, 9, 17 and 26) now specifically recite that the protein coding region encodes an M gene segment protein comprising the sequence set forth in SEQ ID NO:1. Claims having this scope are not taught by the cited prior art references. This alone is believed to overcome this rejection.

Secondly, at the time of our invention, it had not yet been demonstrated that M genome segments of hantaviruses (or any other virus in the family Bunyaviridae) could

elicit immune responses after deposition into the epidermis without a vaccinia virus carrier to initiate infection. As someone having ordinary skill in this art would be aware, it can not be reasonably inferred that a viral antigen from a unique family of viruses will behave the same way as an antigen from a different family in any particular cell. Certainly none of the cited references suggest this; our invention is the first to achieve any immune response elicited by M gene segment proteins in this fashion. In addition, we note that claims 3, 12, 26 and 27 recite specific viruses, such as the Andes virus, the Lagune Negra virus, the Black Creek Canal virus and the Sin Nombre virus. The first descriptions of Andes and Laguna Negra viruses were in 1997, well after all of the cited articles referenced by the Examner. The Black Creek Canal virus was first described in 1995 and the Sin Nombre virus in 1993. It could not have been obvious from these references that these viruses could be protected from before they were even discovered.

Moreoever, it is significant that none of the five references cited by the Examiner disclose or suggest a composition, such as a vaccine, including a carrier particle coated with a polynucleotide comprising a promoter and a protein coding region encoding an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence has at least one antigenic determinant of a hantavirus protein (as claimed in independent claims 1 and 26). And none of the references disclose or suggest methods for using this composition (as claimed in independent claims 9 and 17). None of Schmaljohn, Chu or Arikawa provides any motivation to try to create DNA vaccines whereby the entire M segment is coated onto a carrier particle (claims 1 and 26), or to use these compositions to induce a protective immune response to a hantavirus (claims 9 and 17). Although some of the sequence for the M gene segment was known, at the time of the invention there was no motivation attempting to use this protein coated onto a inert particle to induce protection against infection thereby. Arikawa's statement that their SR-11 M and S genome segment studies may "provide a basis for the thoughtful development of hantavirus recombinant DNA vaccines and diagnostic reagents" is a vague suggestion merely pointing up the need for further research. It would not have been a basis for someone having ordinary skill in this art to predict the claimed DNA vaccine composition (and especially a multivalent vaccine for protection against infection by more than one hantavirus), with any reasonable expectation of success.

At best, the **combination** of these five references would make it obvious to try to achieve any of these embodiments of our invention. As the Examiner noted, neither Schmaljohn nor Chu teaches the combination of a carrier particle onto which is coated a polynucleotide comprising a promoter and a protein coding region encoding an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence has at least one antigenic determinant of a hantavirus protein, or methods of inducing a protective immune response by accelerating the coated particles into epidermal cells.

Vaccines are only useful if they induce protection, and we have the only data to indicate that this can be achieved with the entire M gene segment when coated onto a inert particle after deposition into the epidermis.

At the time our invention was made, one of ordinary skill, upon reading Schmaljohn, Chu, Montgomery, Donnelly, and Arikawa, without hindsight, would not have been motivated toward our invention. Obviousness requires that the art itself motivate the changes necessary to reproduce the invention and that one skilled in the art would expect success from the modification once it was made. Neither requirement – motivation or expectation of success – can be found in the prior art. For those reasons alone, the claims are not obvious within the meaning of 35 U.S.C. §103.

Obviousness of our invention cannot be established by combining the teachings of these two references, absent some suggestion or incentive to support the combination. The mere fact that the vaccine virus-hantavirus of Schmaljohn or Chu may be somehow modified to be coated onto an inert particle and used as a vaccine by gene-gun acceleration into the epidermis does not make the modification obvious unless the references themselves suggest the desirability of the modification. Here, there is no such suggestion, or even incentive, to do so. We respectfully suggest that this is not a fair, or supportable, interpretation of these references. One must "read into" Schmaljohn and Chu (and even more into Montgomery, Donnelly and Arikawa) much of the teaching of our own specification to reach this interpretation. We suggest that a fair reading of these references would not have reasonably suggested the embodiments of our invention.

In summary, we respectfully disagree with the Examiner's suggestion that the deficiencies of Schmaljohn and Chu are overcome by Montgomery, Donnelly and/or

Arikawa. Thus, we believe that all of our claims are patentable over these references, taken alone or in combination.

Having addressed all of the Examiner's outstanding concerns, we submit that this application is in condition for allowance and notice of such is earnestly solicited.

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MARKED-UP VERSION OF CLAIMS AS AMENDED ABOVE

1. (Amended) A composition of matter comprising [a carrier particle] an inert particle suitable for carrying a polynucleotide stably coated thereon; and a [DNA sequence] polynucleotide coated onto the [carrier] particle, the [DNA sequence] polynucleotide comprising a promoter operative in the cells of a mammal and a protein coding region encoding an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one antigenic [coding for a] determinant of a hantavirus protein.

7. (Amended) The composition of claim 1 wherein said [DNA sequence] polynucleotide comprises pWRG-SEO-M.

9. (Amended) A method for inducing a protective immune response to a hantavirus protein in a mammal comprising

(v) preparing a nucleic acid encoding [a] an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one hantavirus protein antigenic determinant [of a hantavirus protein] which is operatively linked to a promoter operative in cells of a mammal;

(vi) coating the nucleic acid in (i) onto [carrier particles] inert particles suitable for carrying a polynucleotide stably coated thereon;

(vii) accelerating the [coated carrier] particles of (ii) into epidermal cells of the mammal in vivo; and

(viii) detecting [a protective] an immune response against viral infection and disease caused by viral infection resulting from (iii) in said mammal upon exposure to a hantavirus.

10. (Amended) The method according to claim 9 wherein the [carrier] particles are gold particles.

16. (Amended) The method according to claim 13 wherein said nucleic acid comprises the sequence set forth in SEQ ID NO:1 and SEQ ID NO:2.

17. (Amended) A method for inducing a protective immune response to a hantavirus infection in a mammal comprising

(v) preparing a nucleic acid encoding [a] an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one antigenic determinant of a first hantavirus protein operatively linked to a promoter operative in cells of a mammal;

(vi) coating the nucleic acid in (i) onto [carrier particles] inert particles suitable for carrying a polynucleotide stably coated thereon;

(vii) accelerating the [coated carrier] particles of (ii) into epidermal cells of the mammal in vivo; and

(viii) detecting an immune protective immune response against viral infection and disease caused by viral infection resulting from (iii) in said mammal upon [a] an exposure to a second hantavirus.

26. (Amended) A [multivalent] vaccine for protection against infection [with] by more than one hantavirus comprising a composition of matter comprising a carrier particle having one or more DNA [sequence] sequences coated onto the promoter operative in the cells of a mammal and a protein coding region coding for [a] an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one antigenic determinant of a [first] hantavirus protein said hantavirus selected from the group consisting of SEOV virus, Dobrava virus, Pumuula virus, Hantaan virus, Sin Nombre virus, Black Creek Canal virus, Bayou virus, New York virus, Andes virus, and Laguna Negra virus.

27. (Amended) The [multivalent] vaccine of claim 26, further comprising a composition comprising a carrier particle having one or more DNA [sequence] sequences coated onto the carrier particle, wherein said one or more DNA sequences each comprise [the DNA sequence comprising] a promoter operative in the cells of a mammal and a

protein coding region coding for [a] an M gene segment protein comprising the sequence set forth in SEQ ID NO:1, which sequence includes at least one antigenic determinant of a second hantavirus different from said first hantavirus, wherein said second hantavirus is selected from the group consisting of Seoul virus, Dobrava virus, Pumuula virus, Hantaan virus, Sin Nombre virus, Black Creek Canal virus, Bayou virus, New York virus, Andes virus, and Laguna Negra virus.